DRUG DELIVERY—PULMONARY DELIVERY

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OVERVIEW

New dispersible formulations and drug aerosol delivery devices for inhaleable peptides, proteins and various small molecules have, in the past decade, become of increasing interest for the treatment of systemic and respiratory diseases. These include, but also extend well beyond, the traditional and long available (although still underutilized) therapies for asthma and chronic obstructive pulmonary disease (COPD). Advances in the use of the lungs as portals for delivery of medication to the blood stream have greatly expanded the potential applications of pulmonary delivery. This advanced technology was initially applied to the systemic delivery of large molecules, such as insulin, interferon-β, or α_1 proteinase inhibitor. By facilitating the systemic delivery of large and small molecule drugs through inhalation deep into the lung, this advanced pulmonary technology provides a unique and innovative delivery alternative for therapies that must currently be administered by injection (i.v., i.m., s.c.) or by oral delivery that causes adverse effects or is poorly absorbed. Indeed, a major advantage of therapy via the lungs is the potentially improved therapeutic index, that is, the ratio of therapeutic benefit to adverse effects. This applies mainly to the therapy of pulmonary disease, but may also be applicable to systemic disease due to reduced first-pass metabolism that may be associated with hepatocellular injury. Pulmonary delivery also offers the potential for better and possibly more economical treatment or prophylaxis of respiratory and systemic diseases (e.g. viral vaccines).

ADVANTAGES OF INHALEABLES

Advanced technology for pulmonary delivery is expanding a category of drugs called "inhaleables," defined as respiratory and systemic therapies administered simply by inhaling. Inhaleables offer several advantages over injectable, transdermal or oral methods of delivery that make them more appealing to both patients and physicians for treating a variety of diseases by means of currently available and future therapies.

First, inhaleables provide a noninvasive method of delivering drugs into the bloodstream for those molecules that currently can only be delivered by injection. These include peptides and proteins, such as insulin for diabetes or interferon beta for multiple sclerosis and most of the drugs developed in recent years by biotechnology companies. Inhale Therapeutic Systems, Inc. (San Carlos, California.) is pioneering advanced pulmonary drug delivery technology to provide a convenient and pain-free alternative to injection for systemic delivery of peptides and proteins. Feedback from patients in the clinical trials and extensive market research support the view that inhaleable drugs will be welcome alternatives to injections.

Second, inhaleables enable effective drug targeting to the lungs for relatively common respiratory tract diseases such as asthma, emphysema, bronchiectasis and chronic bronchitis. This direct delivery most often results in a better treatment outcome while potentially requiring less drug than if given systemically either orally or by injection.

Third, inhaleables provide for very rapid onset of action similar to the i.v. route and quicker than can be achieved with either oral delivery or subcutaneous injections. More rapid delivery could benefit treatments for pain, seizures, panic/anxiety attacks, hypertensive crises, anaphylaxis (severe allergies, food, insect bites), nausea, cardiovascular conditions (arrhythmia, strokes), and Parkinson's "lock-up"—indications where speed is important.

Fourth, inhaling instead of taking pills can help avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects and dosing variability.

MACROMOLECULES AND THEIR IMPORTANCE

Macromolecules are polymers composed of three or more amino acids, sugars, nucleotides, etc. While the large protein molecules are usually made by means of recombinant technologies, the smallest peptides are made primarily by chemical synthesis.

After nearly two decades of activity, innovations in biotechnology and recombinant gene techniques have led to an increase in the approved use of many macromolecule drugs. In recent years, at least 30 macromolecule medications have been approved for marketing in the United States alone, and more than 130 are now in human clinical trials, many for the treatment of chronic and subacute diseases that afflict a large percentage of people worldwide. This is particularly significant, as most of the diseases in question require multiple drug doses and, therefore, multiple injections over many years.

For many years, medical science has been looking for an alternative to injections for the delivery of macromolecule drugs. Due principally to their size, these molecules, mostly proteins and peptides, cannot naturally and efficiently pass through the skin or nasal membranes without the use of penetration enhancers, such as detergents or electrical impulses. If administered orally, they are digested or degraded before they reach the bloodstream. Therefore, oral, transdermal and nasal routes of delivery are inefficient for these molecules. In contrast, research has shown that many of those same molecules are absorbed naturally and quickly into the bloodstream if they are delivered to the deep lung through the use of inhaleables.

WHY IS PULMONARY DELIVERY THE BEST ROUTE?

At best, chronic injection is an unpleasant prospect with a host of hygiene issues and potential side effects. At worst, it can create a barrier to patient compliance with the particular drug regimen required to most effectively treat a given disease, since some patients choose irregular treatment or no treatment at all when faced with frequent injections.

While injection has served as the primary means of delivering macromolecules produced by biotechnology, many noninvasive routes have been explored as alternatives. Oral delivery remains the most common method of delivery for most small molecule drugs. However, oral delivery most often does not work for macromolecules because proteins are digested before they have an opportunity to reach the bloodstream. Commercially successful oral delivery of peptides and proteins has not been achievable with the exception of DDAVP (9 amino acids) and cyclosporin (11 amino acids), two digestion resistant small peptides.

The skin offers an even less naturally permeable boundary to macromolecules than the gastrointestinal tract. Thus, passive transdermal delivery of proteins and peptides using "patch" technology has not succeeded. Peptides and proteins can be shot through the skin into the body using high-pressure "needle-less" injection devices. The devices, which inject proteins like insulin, have been available for years, however they have failed to impress doctors or patients due to the associated discomfort and the potential for "splash back" to transmit blood-borne diseases such as AIDS or hepatitis.

Nasal delivery is inefficient in terms of the amount of drug actually delivered to the body and to increase its efficiency, penetration enhancers must be added that may cause local irritation.

In contrast, research has shown that many molecules are absorbed through the deep lung into the bloodstream naturally with relatively high bioavailability and without the need for enhancers used by other noninvasive routes (1). With regard to the treatment of systemic disease, bioavailability is defined as the amount of drug that actually reaches the bloodstream by any method of delivery, compared to the mass of the agent with which the delivery "device" was charged.

The respiratory tract is accustomed to dealing with chronic exposure to a relatively large load of biological and nonbiological particulates. These are contained in the 20,000 L of air that must be inhaled daily to accomplish gas exchange. It is a tribute to the effectiveness of lung defense mechanisms that in healthy people, for most of their lives, the lungs are sterile below the larynx. According to the American Conference of Governmental Industrial Hygienists, a person can inhale approximately 30 mg/day of inert nuisance dusts into the lung day after day without effect (2), suggesting that the lung is a rather robust organ. Further, there is no evidence that inhaling autologous (self) proteins presents any immune response issues. The high bioavailability provided by the deep lung and the robustness of this organ make it a natural portal of entry for peptides, proteins and other small molecules that could be used to provide systemic therapy.

Riding on Air—Getting to the Deep Lung

The lung provides an enormous surface area through which molecules can be absorbed into the bloodstream. When a breath of air is inhaled, it travels down the trachea and the conducting airways to reach the alveolar epithelium. The conducting airways branch 12–23 times and their surface area measures approximately 0.8 m^2 in adults. The epithelium of the branching airways of the lungs are lined by a relatively thick, ciliated, pseudostratified columnar epithelial layer covered with low viscosity periciliary fluid. Floating above the periciliary

fluid are large "rafts" of thicker gel-like mucus which are propelled towards the pharynx by the rapidly beating cilia.

Once a drug aerosol has made its way through the conducting airways to deposit in the deep lung, the major barriers to entering the body are the 0.15 μm layer of type I alveolar cells that are covered by a very thin layer of epithelial lining fluid consisting mainly of surfactant and the relatively permeable endothelium of the alveolar capillaries. Alveolar cells have so called "tight" junctions that act as a relative barrier to the absorption of large molecules such as proteins and peptides and prevent the development of pulmonary edema.

THE ALVEOLAR EPITHELIUM

The alveolar epithelium measures approximately 100 m^2 in adults—approximately the size of a singles tennis court. It is made up of approximately 500,000,000 tiny airsacs, 300 μm in diameter, called alveoli. These are enveloped by an equally large capillary network and it is across this enormously large and extremely thin (0.1–0.2 μm) membrane that gas exchange and the transcytosis of large and small molecules occurs. The alveolar epithelium is composed of a thin, non-ciliated, nonmucus-covered cell layer consisting mainly of type I and type II fixed alveolar cells. A thin epithelial lining fluid, mainly surfactant, covers the type I and II alveolar epithelial cells.

Type I pneumocytes make up most of the epithelial surface. It is the large, thin, type I pneumocytes that are the primary site of pulmonary protein absorption. The type II pneumocytes, lying in niches between type I cells, are the main source of surfactants and also replace type I cells as they undergo apoptosis (programmed cell death) after about 120 days.

Beneath and extending between these cells are antigen evaluating and presenting dendritic cells. On the epithelial surface are motile phagocytes called macrophages, about 15 to each alveolus. These remove foreign biological and non-biological particles and assist in maintaining the sterility of the alveolar surface. Macrophages are the immune system's first line of defense against inhaled organisms. The key to preventing macrophages from engulfing inhaled drug particles is solubility. Ideally, drugs are rapidly dissolved in the epithelial lining fluid on the surface of the epithelium thus assisting their ingestion by macrophages. This process can be accelerated by means of small, drug-containing, lipid particles.

TRANSCYTOSIS

The body absorbs peptides and proteins into the bloodstream by a natural process known as transcytosis, which occurs deep in the lung. Transcytosis allows drug molecules to move across an impermeable cell membrane without creating holes in the cells and destroying the barrier (Fig. 1).

The process is performed by trillions of tiny membrane bubbles, or transcytotic vesicles, which form from invaginations of the cell membrane on one side of the cell and fuse back into the membrane on the other side of the cell. The result is that small volumes of alveolar fluid, containing dissolved proteins, are rapidly carried by a "bucket brigade" from one side of the alveolar cell to the other.

Small molecules and peptides are also thought to be absorbed through the lung surface by an analogous process called paracellular transport. This is achieved through the tight junctions which connect cells to each other. However, in contrast to transcytosis that is rapid and efficient, paracellular transport is slow and inefficient.

Many dissolved proteins that have been transported through the alveolar cells are rapidly reabsorbed into the blood through the capillary endothelial cells (also by

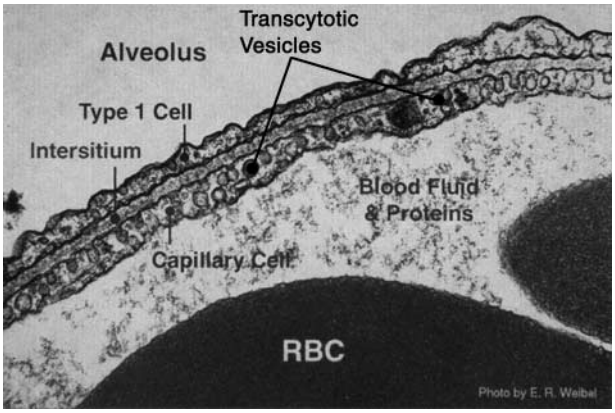

Fig. 1 Natural absorptive mechanism. The body absorbs peptides and proteins into the bloodstream by a natural process known as transcytosis which occurs deep in the lung. Transcytosis is the process by which large molecules move across an impermeable cell membrane without creating holes in the cells and destroying the barrier. It is performed by tiny membrane bubbles, or transcytotic vesicles, which form invaginations of the cell membrane on one side of the cell and dissolve back into the membrane on the other side of the cell. The result is that small volumes of alveolar fluid, including dissolved proteins, are carried by a "bucket brigade" from one side of a cell to the other.

transcytosis). In the case of some large proteins, they are more slowly drained across the interstitial space by means of the pulmonary lymphatics, which also empty into the bloodstream via the thoracic duct and superior vena cava.

The purpose of transcytosis in lung biology is not clearly understood. It is thought to be a natural mechanism for controlling the level of airway fluid and for moving endogenous proteins back and forth across the epithelium during normal physiological "housekeeping." Both transcytosis and paracellular transport are sophisticated cell processes mediated by complex cell machinery.

The result of these two processes is a noninvasive means of delivering proteins and peptides to the bloodstream with relatively high bioavailability and without the use of penetration enhancers (3).

Because the molecules are delivered rapidly into the bloodstream, there is a much more rapid onset of action than with any other non-i.v. delivery method. This can be particularly useful in indications where speed is important such as pain control, relief of muscle spasm, panic/anxiety attacks, hypertensive crises, cardiac arrythmias, anaphylaxis (severe allergies to food and insect bites), nausea, cardiovascular conditions (arrhythmia, strokes), Parkinson's "lock-up," and epileptic seizures.

Characteristics of Lung Absorption

Large, highly vascularized area available for transcytosis
Conducting airways $\sim$0.8 m^2
Alveoli $\sim$80 m^2
Alveoli highly permeable to many biologics; most small molecules and many macromolecules capable of absorption throughout the respiratory tract
Relatively rapid, first-order absorption
Much less first-pass metabolism and degradation in the gastrointestinal tract and liver
Cytochrome P450 enzyme concentration in human lungs $<$0.7% that of liver
Only 1A1 and 4B1 P450 isozymes reported in the human lung

CLINICAL APPLICATIONS OF PULMONARY DELIVERY

Pulmonary drug delivery in our post-genomics era has opened the door to noninvasive administration of a wide variety of macromolecules. Since drug delivery by the pulmonary route is now practical, drug companies can reconsider the development of new macromolecules and small molecules whose markets are limited as an injectable or when given by mouth. Furthermore, rather than spending years to develop an oral version (or abandon a project altogether) especially for chronic or subchronic therapies, pharmaceutical companies can save years of development time by using pulmonary delivery for their macromolecule drugs. Pulmonary delivery could also replace some oral drugs due to the much faster onset of action with improved absorption and avoidance of first pass losses with delivery through the GI tract.

Nearly every biotherapeutic product involving chronic or longterm use would benefit from noninvasive delivery, which could provide pharmaceutical companies with a competitive advantage, expand the market for products and/or enable new indications to be considered. Further, proprietary new inhalation delivery systems can extend the patent life of a drug, increase patient compliance and possibly reduce healthcare costs.

Because of the advances in biotechnology that have resulted not only in new macromolecules but also in new devices to deliver them via the lungs, patients and physicians will soon be able to use this route to treat diseases such as diabetes, hepatitis, osteoporosis, multiple sclerosis, genetic emphysema, cystic fibrosis, and other pulmonary infections among others.

Pulmonary delivery could also be used for delivery of vaccines. In the United States alone, children endure as many as 14 vaccine injections by age 16 and that number is climbing as new research makes more vaccines available. The cost of a single injection can quadruple if the costs of equipment and personnel are included. Furthermore, fear of needles reduces compliance, thus the potential for an increased market share in this area. Inhaled vaccines may be used to prevent influenza, pneumonia, tuberculosis, measles, cytomegalovirus, asthma, and mucosal-entry diseases such as sexually transmitted diseases including HIV.

PULMONARY DISEASE AND PULMONARY DELIVERY

Pulmonary drug targeting has long been used to treat lung disease, particularly asthma and COPD, non-CF and CF bronchiectasis, bronchiolitis and recently influenza. Potentially, other pulmonary diseases such as parenchymal fibrosis, acute bronchitis, pneumonia and even carcinoma of the lung in situ might be treated by inhalation. Secondary lung malignancies have been treated by inhalation of Il2 and GM-CSF with some benefit.

With regard to pulmonary infections, much higher concentrations of antibiotics can be achieved in the lungs

by inhalation, which should accomplish greater and more rapid bacterial killing with less likelihood of developing bacterial resistance. Furthermore, topical delivery achieves reduced systemic side effects for equivalent therapeutic benefit.

CHALLENGES AND SOLUTIONS IN PULMONARY DELIVERY

In the mid-1950s the first pressurized metered dose inhaler (MDI) was developed for the administration of bronchodilator drugs locally to the lung. It was a major advance for the treatment of asthma since it made aerosol medications readily available in an inexpensive small multidose device.

The world aerosol market has grown due to the increased incidence of asthma and chronic obstructive pulmonary disease (COPD) as well as due to an increased number of patients receiving aerosol medications as the drug formulation-device combination of choice. Until recently, companies developed pulmonary drug delivery systems primarily to dispense drugs to the airways of the lung for local lung applications. Application systems such as pressurized metered dose inhalers (pMDIs), breath activated dry powdered inhalers (DPIs), liquid jet and ultrasonic nebulizers have proved useful in the management of airway inflammation and bronchoconstriction.

For the systemic delivery of most drugs, however, currently marketed aerosol delivery systems are inadequate due to the following:

1. *Low System Efficiency:* To be commercially feasible for the administration of costly proteins and peptides, the overall efficiency of presently available systems has remained generally too low. Correct aerosol particle size is very important for optimum deep lung delivery. Studies have established that these particles should range from one to three microns in aerodynamic diameter for optimum lung deposition efficiency. If the particles are too large, they impact in the oropharynx and larynx. If they are too small, they will be exhaled. Most existing MDI systems can only deliver a small fraction (about 10–20%) of the dispensed drug in the correct particle size for deep lung deposition (4–6) although, recently developed 1 μm solution aerosols from corticosteroid pMDIs have achieved lung deposition efficiencies of 60% or more.
2. *Low Drug Mass per Puff:* With most existing systems, the total amount of drug per puff delivered to the lower respiratory tract is too low—less than 1000 mcg (6)—to enable practical delivery of many macromolecules which require milligram doses. Device payload versatility is an important feature with the new macromolecule drugs since they come in a wide variety of potencies—from a few micrograms per dose to tens of milligrams. Traditional inhalation systems have primarily been designed to deliver some of the most potent drugs in use today, namely the inhaled bronchodilators and corticosteroids used for treating asthma. Both of these classes of medication are bioactive in the lung at 5–50 μg/dose. In contrast, many peptide and protein drugs require deep lung doses in the 2–20 mg/dose range (1).
3. *Poor Formulation Stability for Macromolecules:* existing aerosol systems are not designed to protect the formulations of delicate macromolecules. Most traditional small molecule asthma drugs are crystalline and, in the case of corticosteroids, relatively moisture resistant in the dry state. They are also rather stable in liquids as compared to most macromolecules, which are unstable in the liquid state, amorphous, and highly moisture sensitive in the dry state. There are exceptions, including Genentech's Pulmozyme, the first FDA approved aerosol protein, a 33 kDa digestive enzyme (DNAse) used to break up the thick, grossly infected, mucus in cystic fibrosis. It is available as a stable liquid formulation for nebulization. Other proteins such as growth hormone, G-CSF and Interferons aggregate and are partially denatured by nebulization (7).
4. *Poor Dosing Reproducibility:* for a variety of reasons, the dosing reproducibility of many existing systems is too variable for systemic delivery of most macromolecule drugs (6, 8). Physicians and patients alike have tolerated the highly variable dosing of inhaled asthma medications for years because the drugs have a wide therapeutic window and optimizing the drug dose is usually a matter of trial and error. In the case of the bronchodilators, the rapid improvement characterized by easier breathing has enabled patients to know whether or not they have used the proper inhalation technique and dose. So far, no macromolecule drug appears to possess such rapid biofeedback.

Potential solutions to these challenges to ensure effective inhalation drug treatment include active dry powder delivery systems, active liquid blister technology, and hydrofluorocarbon (HFC) propellant nebulization systems.

Dry Powder Inhalation (DPI) Systems

Dry powder aerosols are frequently highly soluble and quickly dissolve in the fluid layer lining the surface of the deep lung before passing through the thin cytoplasm of the

type I alveolar cells the interstial "space" and capillary endothelium. The main advantages of dry powder systems include product and formulation stability (even at room temperature or above), the potential for delivering a low or high mass of drug per puff, low susceptibility to microbial growth, and applicability to both soluble and insoluble drugs.

Current challenges facing the development of these systems for macromolecules include moisture control, efficient powder manufacturing, reproducible powder filling, unit dose packaging and development of efficient reliable aerosol dispersion and delivery devices.

One of the challenges is that the fine powder particles tend to stick to each other. These clumps can be difficult to break apart into breathable particles for slow inhalation by the patient. Breath-powered powder inhalers for asthmatics attempt to apply the forces generated by a rapid forceful inspiration to break apart the powder clumps. But vigorous rapid inhalation does not efficiently deaggregate and target the very fine powder clumps to the deep lung. This is mainly because particle inertia causes impaction of most of the medication in the oropharynx.

One solution to the clumping problem for macromolecule drug delivery is to use a device with sufficient power to force the deaggregation of even fairly adhesive powders. One company working on this issue, Inhale Therapeutic Systems, of San Carlos, California, has designed a device that uses sonic velocity compressed air (1.5 mL) to aerosolize the powder (Fig. 2). Systemic Delivery. These de-agglomerated particles form a standing cloud in an aerosol holding chamber. The patient then inhales the stationary cloud with one slow, rate controlled deep breath, eliminating the need for patient coordination between the generation of the aerosol powder and inhalation. Furthermore, the slow deep breath encourages efficient alveolar delivery of the drug.

The keys to efficient aerosol targeting to the deep lung are:

1. Formulation of readily dispersible powders by particle engineering
2. A device that is small, inexpensive and user-friendly to generate the drug aerosol, and
3. Inhalation at a low inspiratory flow rate (below 20 L/min) to minimize upper airway and large airway deposition.

Fig. 2 Advanced inhaler technology for pulmonary systemic delivery. Shown here: a collapsed and extended advanced inhaler used for systemic delivery. A patient would use this device and powdered medicine instead of receiving an injection or taking a pill. The device slides open and closed like a telescope for compact carrying, making it portable for patients who must self-administer drugs regularly. A patient would open the device, insert a blister of powdered medicine and then pump the handle which compresses a small amount of air inside the device. By pushing a button, the patient causes the compressed air to be released at extremely high velocity, breaking apart the powder from the blister and sending it into the 200-mL chamber where it is captured as a stationary cloud. When patients inhale this fine powder formulation of the drug as an aerosolized cloud, they receive the medicine first and then a volume of air that helps push the drug deep into the lung, where it is absorbed into the blood.

Liquid Systems

Liquid systems provide ease of filling and availability (in some cases) of preexisting injectable formulations for macromolecules. These systems, however, also pose hurdles for their use with protein and peptide drug delivery. They currently offer lower drug payload per puff than dry systems (because more than 95% of the mass is

water), difficulty in formulation stabilization (particularly for insoluble drugs), and greater susceptibility to microbial growth within a device. Current challenges facing the development of liquid systems for macromolecules are formulation stability, unit dose packaging, high payload delivery and development of efficient reliable devices.

One of the oldest medical aerosol delivery systems is the air jet nebulizer, which forms a fine mist of liquid droplets from a drug solution that a patient breathes over a period of 10–30 min/dose. The cumbersome electric powered jet nebulizer is often used as a fallback delivery system for asthmatics who do not appear to be getting relief from the small portable MDIs and DPIs. Nebulizers are very hard on macromolecules and cause aggregation in the device before some macromolecules can be inhaled (7).

Some companies are focusing on the development of a new generation of liquid systems that are portable, more efficient, more gentle on the macromolecule and that can deliver the medicine in far fewer puffs than the old fashioned nebulizer. Two companies who are developing advanced pulmonary delivery liquid systems are Aradigm Corporation, Hayward, CA, and AeroGen, Inc., Sunnyvale, CA.

Propellant Systems

The best example of propellant-powered systems is the well-known little canister inhalers (pressurized metered dose inhalers or pMDIs) used by asthmatics since the 1950s. The original, ozone-depleting chlorofluorocarbon (CFC) propellants are being replaced by the more environmentally friendly hydrofluorocarbons (HFCs). HFC propellant systems give patients the convenience of small, inexpensive multidose devices that can be filled easily. However, they appear at this time not to be amenable to stable formulating of macromolecular therapeutic applications. Current designs deliver low payloads per puff, have low lung delivery efficiency, poor stability for water-soluble macromolecules and moderately high dosing variability (6).

OTHER ISSUES REGARDING PULMONARY DELIVERY

Notwithstanding the scientific advances in this field, many still have concerns about acceptable bioavailability and reproducibility with pulmonary delivery while others harbor some fears about the safety of deep lung inhalation of macromolecules.

Dose reproducibility: Several human studies comparing aerosol insulin administration to subcutaneously administered insulin showed that the variability in glucose response from a liquid nebulizer that utilized the standing cloud concept was equivalent or better than that seen with insulin injection (9). Inhale Therapeutics Systems, Inc. has adopted this standing cloud concept for its dry powder inhaler to achieve reproducibility of delivery of macromolecules to the systemic circulation that is equivalent to subcutaneous injections.

Safety: A growing body of data indicates that inhaling proteins can be safe, whether the patient has healthy lungs or a pulmonary disease (see Table 1). With relatively stable lung diseases, unless the damage or deterioration of the lung parenchyma is very severe—that is, if the patient has lost over 60% of lung function—most researchers do not expect systemic variability from pulmonary delivery to differ from that seen with injections. With typical upper respiratory diseases such as colds and flu, lung function is thought to remain within 70–100% of normal. Even with a cold or flu where inspiratory capacity can fall up to 30% below normal, a deep breath that is 70% of a normal deep inspiration can deliver the aerosol drug into the lungs if the standing cloud technique is used to provide an aerosol bolus at the very beginning of a slow deep breath.

Despite considerable clinical experience with aerosolized macromolecules, there have been no serious safety issues to date, nor have there been significant problems with throat irritation or cough. So far, the proteins and peptides under development for human applications have

Table 1 Aerosol safety of peptides and proteins

Molecule	Study[a]
Insulin	89 patients 24 months
DNase	Approximately 10,000 patients Almost four years
Heparin	544 patients 1 day to 1.3 years
Interferon-α	16 patients Up to 67 weeks
Leuprolide acetate	Hundreds of patients 6 months
α_1-Antitrypsin	12 patients 1 day; 1–7 days
Antibiotics	Hundreds of patients Up to 2 years
Interferon-γ	5 patients 12 days

[a]None of these studies had any adverse effect on lung.
(From Refs. 10–17.)

been virtually tasteless and the incidence of cough, with properly formulated drugs, has been very low. However, large particle sizes (more than 5 μm) can cause cough regardless of chemical composition, so it is important that particle sizes be kept in the so-called fine particle range (i.e., less than 5 μm).

Given the advances in pulmonary delivery technology, the issues for drug companies and patients concerning pulmonary delivery revolve around economic evaluations, approvals, administration and managed health care. As these issues are resolved, pulmonary delivery will doubtless become regarded as one of the leading drug delivery alternatives.

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